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# Preparation of 3-aryl-substituted salicylaldehydes via Suzuki coupling

Michael A. Zhuravel and SonBinh T. Nguyen*

*Department of Chemistry, Northwestern University, Evanston, IL 60208, USA*

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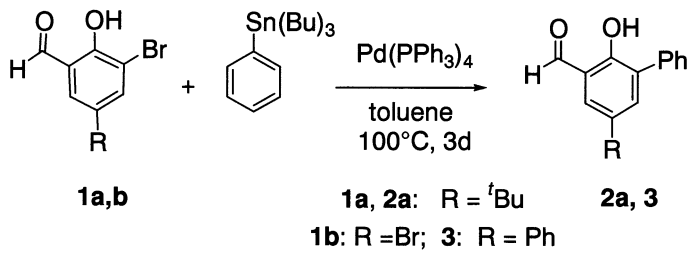
**Abstract**—An efficient method for the preparation of 3-arylsalicylaldehydes by palladium-catalyzed cross-coupling reaction of arylboronic acids and 3-bromo-5-*tert*-butylsalicylaldehyde is described. Parallel catalyst screening allowed rapid optimization of the reaction conditions. © 2001 Published by Elsevier Science Ltd.

In the course of studying asymmetric catalysis with metal salen complexes we became interested in the preparation of 3-aryl-substituted salen ligands. The steric properties of 3-substituents in salen ligands can significantly influence the stereochemical outcome of asymmetric reactions. For example, transition metal cyclopropanation catalysts generally produce *trans* products as the predominant isomer.[1–3] However, it has been shown that incorporation of bulky aryl groups in the 3-positions of the salen aryl rings can lead to reverse selectivity in Ru(salen)-catalyzed olefin cyclopropanation to give the *cis*-isomers.[4–6] While seemingly simple, salicylaldehydes that serve as precursors to 3-aryl-substituted salen ligands are not common, especially those which also bear an alkyl moiety in the 5-positions. Bulky 5-alkyl substituents, especially 5-*tert*-butyl, have been shown to be essential for high selectivity in asymmetric catalysis with metal salen complexes.[7] With these criteria in mind we set out to search for a general synthetic route to 3-aryl-5-*tert*-butyl aldehydes.

There are few reports on the synthesis of 3-aryl-substituted salicylaldehydes. The approach most commonly used involves the initial preparation of 3-arylphenols followed by formylation. For example, Grubbs et al. prepared 3-(9-anthracenyl)salicylaldehyde by Ni-catalyzed coupling of an aryl Grignard reagent (formed from protected 2-bromophenol) and aryl halide followed by formylation.[8] The overall yield of this sequence of reactions can be improved if the protection/deprotection steps are avoided. A simple solution would entail the direct coupling of salicylaldehydes with aryl precursors using functional group-tolerant Pd-mediated cross-coupling which has been shown to be a powerful tool for the synthesis of biaryls.[9] Since we were interested in a general method to prepare 3-aryl-5-*tert*-butyl-substituted aldehydes, we decided to investigate this reaction as it would allow us to achieve several different 3-aryl-substituted salicylaldehydes in one step from the readily available 3-bromo-5-*tert*-butylsalicylaldehyde.

Chan and co-workers have synthesized 3-(2-pyridyl)-5-*tert*-butylsalicylaldehyde via Stille coupling.[10] In our hands, the reaction of either 3-bromo-5-*tert*-butylsalicylaldehyde (**1a**) or 3,5-dibromosalicylaldehyde (**1b**) with $PhSnBu_3$ (Eq. (1)) gave the desired 3-phenyl-5-*tert*-butylsalicylaldehyde (**2a**) and 3,5-diphenylsalicylaldehyde (**3**) in 67 and 48% yields, respectively. While relatively successful, the Stille reaction required prolonged heating (72 h) at high temperatures (>100°C). These drawbacks led us to consider Suzuki coupling as an alternative.




**1a,b** **1a, 2a**: R = $^t$Bu **2a, 3**

**1b**: R =Br; **3**: R = Ph

(1)

* Corresponding author. Tel.: 847.467.3347; fax: 847.491.5123; e-mail: stn@chem.northwestern.edu

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During the last decade, Pd-catalyzed coupling of aryl halides and organoboron compounds has undergone rapid development. New protocols have appeared that allow effective and rapid reactions under very mild conditions.[11,12] Unlike organostannanes, organoboronic acids are generally solid and nontoxic. Their wide commercial availability is an added advantage. However, the coupling conditions tend to vary widely depending on the steric and electronic properties of the substrate and often have to be individually optimized. To reduce the time required to optimize the coupling conditions, we carried out parallel reactions in a 12-well heating block (Thermolyne 17600). Reaction on a scale of up to 0.5 mM can be conducted in this fashion using 8 mL vials (equipped with magnetic stir bar and a Teflon-lined septum-screw cap for ease of sampling). Analysis can be performed quickly by either gas chromatography or $^1$H NMR spectroscopy. The results of three such parallel runs for the coupling of **1a** and $PhB(OH)_2$ are summarized in Table 1.

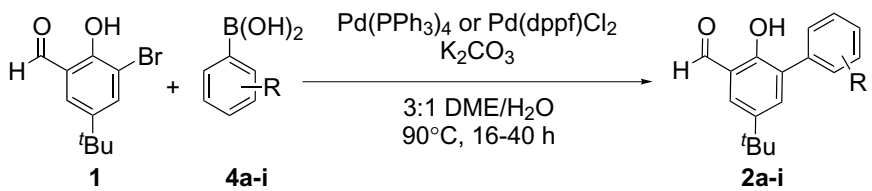
Of the catalysts used, $Pd(dppf)Cl_2$ and $Pd(PPh_3)_4$ exhibited the highest activity in the presence of $K_2CO_3$ as a base, and mixture of DME/water (3:1) as a solvent. We selected conditions reported in entries 5 (method **A**), 6 (method **B**) and 9 (method **C**) as primary candidates for further investigation. Additional experiments showed that the synthesis of **2a** using these methods could be achieved in less than 3 h.

Having established the synthetic protocol for preparation of our target products, we turned our attention to other substituted phenylboronic acids. A series of 3-substituted salicylaldehydes was prepared using methods **A**–**C** and characterized by $^1$H and $^{13}$C NMR spectroscopy (Eq. (2)). The results of these experiments are reported in Table 2. Salicylaldehydes **2a**–**f** and **2i** were obtained in excellent yields by using method **A**. Methods **B** and **C**, however, gave no product when applied to the synthesis of **2e**. All three methods failed to produce **2g** and **2h**. Instead, dehydroxyborylation products were observed in these two cases. We then tried to prepare **2a** and **2e**–**h** employing a protocol outlined by Fu and co-workers, which allows coupling of boronic acids and aryl halides under mild conditions using $Pd_2(dba)_3/P(^tBu)_3$ as a catalyst and KF as a base.[11] This method converted **1a** into **2a** in good yield at room temperature but did not give good results with the other substituted substrates. Raising the reaction temperature to 50°C improved the yields of **2e** and **2f** but did not give **2g** or **2h**. Suspecting that the formyl group may be the cause behind the coupling difficulties, we decided to employ a post-coupling formylation strategy

**Table 1.** Effect of reaction conditions on the Pd-catalyzed coupling of 3-bromo-5-*tert*-butyl salicylaldehyde and phenylboronic acid

| Entry | Catalyst | Base | Solvent[a] | Temperature (°C) | Time (h) | Conversion (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | $Na_2CO_3$ | Toluene | 90 | 40 | 50 |
| 2 | $Pd(PPh_3)_4$ | $K_2CO_3$ | Toluene | 60 | 40 | 78 |
| 3 | $Pd(PPh_3)_4$ | $Na_2CO_3$ | DME/water | 60 | 40 | 100 |
| 4 | $Pd(PPh_3)_4$ | $K_2CO_3$ | Toluene | 90 | 40 | 93 |
| 5 | $Pd(PPh_3)_4$ | $K_2CO_3$ | DME/water | 90 | 16 | 100 |
| 6 | $Pd(PPh_3)_4$ | $K_2CO_3$ | Dioxane | 90 | 16 | 100 |
| 7 | $Pd(PPh_3)_4$ | $Cs_2CO_3$ | Toluene | 90 | 40 | 83 |
| 8 | $Pd(dppf)Cl_2$[b] | $Na_2CO_3$ | DME/water | 60 | 40 | 78 |
| 9 | $Pd(dppf)Cl_2$[b] | $K_2CO_3$ | DME/water | 90 | 16 | 100 |
| 10 | $Pd(PCy_3)Cl_2$ | $Na_2CO_3$ | Dioxane | 90 | 40 | 30 |
| 11 | $Pd(PCy_3)Cl_2$ | $K_2CO_3$ | DME/water | 90 | 40 | – |
| 12 | $Pd(OAc)_2/PCy_3$ | $K_2CO_3$ | Dioxane | 90 | 40 | 69 |
| 13 | $(Pd(P^tBu_2(OH))_2Cl)_2$ | $K_2CO_3$ | Dioxane | 90 | 40 | 55 |
| 14 | $(Pd(P^tBu_2(OH))_2Cl)_2$ | $Cs_2CO_3$ | Dioxane | 90 | 40 | 81 |
| 15 | $(Pd(P^tBu_2(OH))_2Cl)_2$ | KF | Dioxane | 90 | 40 | 43 |
| 16 | $(Pd(P^tBu_2(OH))Cl_2)_2$ | $Cs_2CO_3$ | Dioxane | 90 | 40 | 68 |
| 17 | $(Pd(P^tBu_2(OH))Cl_2)_2$ | CsF or KF | Dioxane | 90 | 40 | – |

[a] DME = dimethoxyethane.
[b] dppf = diphenylphosphinoferrocene.
[c] Determined by GC analysis using HP-5 column.

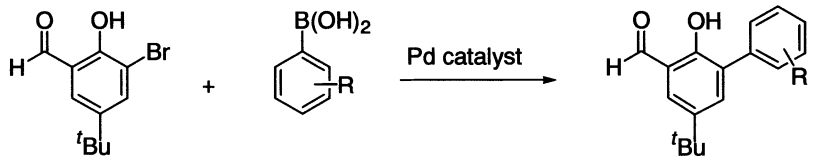


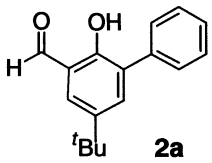
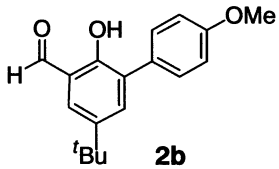
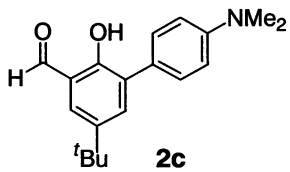
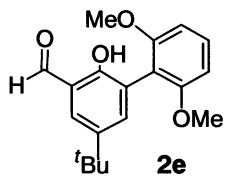
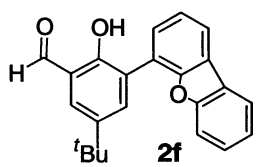
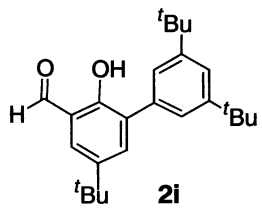

**1** **4a-i** **2a-i**

**4a, 2a**: R = H
**4b**, **2b**: R = 4-OMe
**4c**, **2c**: R = 4-$NMe_2$
**4d**, **2d**: R = 4-COOH
**4e**, **2e**: R = 2,6-$(OMe)_2$
**4f**, **2f**: R = 1-Benzofuranyl
**4g**, **2g**: R = 2,4,6-tris(*tert*-butyl)phenyl (Mes*)
**4h**, **2h**: R = 9-Anthracenyl
**4i**, **2i**: R = 3,5-$(^tBu)_2$

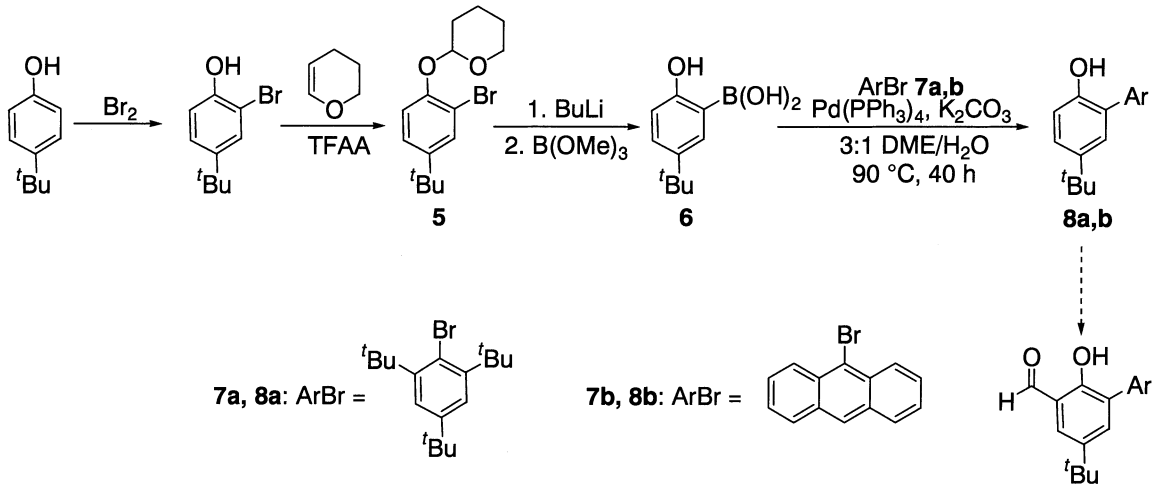
(2)

**Table 2.** 3-Aryl-5-*tert*-butyl salicylaldehydes via Suzuki coupling




| Method | Product | Yield (%)[c] | NMR DATA |
|---|---|---|---|
| A[a] |  **2a** | 84 | $^1$H NMR (300 MHz, $CDCl_3$): δ 11.35 (1H), 9.92 (1H), 7.65-7.28 (m, 7H), 1.36 (9H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 197.1 (*C*HO), 156.8, 142.9, 135.9, 129.6, 129.5, 129.0, 128.9, 128.5, 127.8, 120.5, 32.0 (*C*Me$_3$), 31.7 (C*Me*$_3$). |
| A[a] |  **2b** | 88 | $^1$H NMR (300 MHz, $CDCl_3$): δ 11.32 (1H), 9.90 (1H), 7.59 (d, 1H, *J* = 2 Hz), 7.50 (d, 2H, *J* = 8 Hz), 7.46 (d, 1H, *J* = 2 Hz), 6.96 (d, 2H, *J* = 8 Hz), 3.82 (3H), 1.33 (9H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 197.1 (*C*HO), 159.2, 156.8, 142.8, 135.6, 130.6, 129.8, 129.1, 120.4, 114.0, 55.7 (O*Me*), 34.8(*C*Me$_3$), 31.7 (C*Me*$_3$). |
| A |  **2c** | 86 | $^1$H NMR (300 MHz, $CDCl_3$): δ 11.32 (1H), 9.90 (1H), 7.59 (d, 1H, *J* = 2 Hz), 7.50 (d, 2H, *J* = 8 Hz), 7.46 (d, 1H, *J* = 2 Hz), 6.96 (d, 2H, *J* = 8 Hz), 3.82 (3H), 1.33 (9H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 197.1 (*C*HO), 157.0, 150.1, 142.7, 135.4, 130.3, 130.1, 128.4, 124.8, 120.4, 112.5, 41.0 (N*Me*$_2$), 34.6 (*C*Me$_3$), 31.7(C*Me*$_3$). |
| A<br>B[b] |  **2e** | 91<br>0 | $^1$H NMR (300 MHz, $CDCl_3$): δ 11.01 (1H), 9.89 (1H), 7.48 (m, 2H), 7.30 (m, 1H), 6.64 (d, 2H, *J* = 8 Hz), 3.72 (6H), 1.32 (9H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 196.9 (*C*HO), 158.2, 157.7, 141.8, 138.3, 129.7, 129.4, 128.4, 123.2, 120.1, 104.5, 56.4 (O*Me*), 34.5 (*C*Me$_3$), 31.7(C*Me*$_3$). |
| A |  **2f** | 72 | $^1$H NMR (300 MHz, $CDCl_3$): δ 11.32 (1H), 9.97 (1H), 7.97-7.90 (m, 2H), 7.65-7.20 (m, 6H), 1.38 (9H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 197.0 (*C*HO), 157.3, 156.2, 142.6, 137.0, 132.3, 132.2, 130.3, 128.9, 127.4, 124.8, 124.5, 123.0, 122.9, 121.4, 120.9, 120.6, 120.5, 112.0, 34.7 (*C*Me$_3$), 31.7(C*Me*$_3$). |
| A |  **2i** | 71 | $^1$H NMR (300 MHz, $CDCl_3$): δ 11.35 (1H), 9.97 (1H), 7.70 (d, 1H, *J* = 2 Hz), 7.54 (d, 1H, *J* = 2 H), 7.49 (m, 1H), 7.46 (m, 2H), 1.41 (18H), 1.40 (9H). $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 197.1 (*C*HO), 157.0, 150.6, 142.7, 136.1, 136.0, 131.2, 129.3, 123.9, 121.9, 120.3, 35.4 (*C*Me$_3$), 34.6(*C*Me$_3$), 32.0 (C*Me*$_3$), 31.8 (C*Me*$_3$). |

[a]Arylboronic acid (1.1 equiv.), $K_2CO_3$ (1.5 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.) heated at 90°C for 16–40 h in $N_2$-degassed DME:$H_2O$ (3:1 v/v).
[b]Arylboronic acid (1.1 equiv.), $K_2CO_3$ (1.5 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.) heated at 90°C for 16–40 h in $N_2$-degassed dioxane.
[c]Yields are given for pure products isolated by flash chromatography on silica gel. The purity of products was assessed by $^1$H and $^{13}$C NMR spectroscopy and GC analysis.




**Scheme 1.**

(Scheme 1). Thus, 2-hydroxy-5-*tert*-butylboronic acid (**6**) was prepared and reacted with Mes*Br (**7a**) and 9-bromoanthracene (**7b**) using method **A** (Scheme 1). However, this approach also did not yield the desired products. Formation of small amounts of **8a** was observed by GC/MS but no **8b** was detected. Analysis of the reaction mixtures shows mostly starting materials and, in the case of **7b**, also some anthracene. We note that Grubbs and co-workers have been able to prepare 2-(9-anthracenyl)phenol via Kumada coupling under extended reaction time (4 days, THF reflux) albeit in moderate yield.[8,13]

In conclusion, we have shown that the Suzuki coupling between a variety of arylboronic acids and 3-bromosalicylaldehydes is a general and direct method to access several functionalized 3-arylsalicylaldehydes. While highly efficient in the case of sterically hindered substituents, the reaction is unsuccessful when very bulky aryls such as Mes* are used. A parallel strategy using the Thermolyne 12-well heating block leads to a significant reduction of time in the search for optimized reaction conditions.

## Acknowledgements

We thank Dr. George Y. Li (DuPont Central Research) for providing us with samples of $(Pd(P'Bu_2(OH))_2Cl)_2$ and $(Pd(P'Bu_2(OH))Cl_2)_2$.[14] Financial support from the Dreyfus Foundation, the DuPont Company, and the Packard Foundation is gratefully acknowledged.

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